

Evaluation of factors (body mass index status, hypertension and diabetes mellitus) associated with Venous thromboembolism (VTE)

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ABSTRACT

The role of injectable contraceptives as a risk factor for venous thromboembolism is controversial. The aim of the study was to determine the risk of thrombosis associated with the use of injectable contraceptives in Port Harcourt, Nigeria. This is a hospital based cross sectional comparative study. In this study the number of cases that were hypertensive and diabetic were significantly higher than controls. This may be related to the higher mean age of the case group compared to the control group because injectable contraceptives do not contain estrogen which is implicated in increased risk of hypertension and diabetes. Hypertension and diabetes mellitus are independent predictors of venous thromboembolism. It is important to note that the comparative risk of VTE was not significantly different between both groups. Normal platelet counts, d-dimer and fibrinogen suggest that the risk of thrombosis in women on injectable contraceptives is not increased, therefore injectable contraceptive use may not be associated with increased thrombotic risk. It is therefore recommended that routine screening of women on injectable contraceptives for VTE may be unnecessary. Larger population-based local studies to validate these results are required.

Keywords: Venous thromboembolism, BMI, hypertension and diabetes

INTRODUCTION

Thrombosis is the end product of an imbalance between procoagulant, anticoagulant and fibrinolytic factors which could be arterial or venous [1, 2]. It is commonly associated with some risk factors and occurs more frequently with increasing age [3]. Arterial thrombosis, which is mainly determined by changes in vessel wall in particular atherosclerosis are seen more frequently with ischaemic stroke and myocardial infarction [4]. Due to the blockage of blood flow, symptoms of arterial thrombosis are seen as acute,

however it is a chronic disorder related to a slowly increasing severity of atherosclerosis [5]. Contraception is an intentional prevention of conception through the use of various devices, sexual practices, chemicals, drugs, or surgical procedures [5]. Previous studies have shown that hormonal contraceptives have effects on thrombus formation, especially the combined oral contraceptive pills [6]. Injectable contraceptives were reported to be associated with a small risk of venous thromboembolism. There are

controversies on the association between thromboembolism and progesterone-only (injectable contraceptives) [7]. One school of thought believes there is an association, while the other does not [8]. There is however a paucity of studies done in our environment on the risk of developing thrombosis with the use of injectable contraceptives [9, 10]. Venous thrombosis on the other hand manifests as deep venous thrombosis (DVT) and or pulmonary embolism (PE) [6]. It commonly affects the lower extremities but could also affect the upper extremities or rarely manifest as intra-abdominal DVT [7].

Prothrombin gene mutation: This is also called the prothrombin gene mutation G20210A [11]. It is a common prothrombotic single nucleotide polymorphism. The risk of VTE is three times higher in patients with this mutation because of the increased level of prothrombin in the blood [12].

Protein C deficiency: This is a rare genetic disorder that predisposes one to the formation of venous clots due to absence or reduced levels of the natural anticoagulant [13]. **Protein C:** It is inherited in an autosomal dominant fashion [13]. **Protein S deficiency:** This is

a rare but potent risk factor for venous thromboembolism. Protein S is a co-factor for Protein C, therefore its absence or deficiency limits natural anticoagulation activity of protein C. Deficiency is an important cause of thrombophilia [14].

Antithrombin deficiency: It is a relatively rare genetically acquired trait, also the first inherited trait associated with thrombophilia. It is inherited in an autosomal dominant fashion [15].

Dysfibrinogenemias: They are a group of autosomal dominant disorders characterized by qualitative abnormalities of fibrinogen. With some variant associated with an increased risk of thrombosis and can be detected by a prolonged thrombin time [16].

Homozygous homocystinuria: Homocystinuria due to homozygous cystathionine beta-synthase deficiency. It is an inborn error of metabolism characterized by a high risk of thrombosis and premature atherosclerosis [17].

Factor XII deficiency: Affected individuals show a prolonged activated partial thromboplastin time but they do not bleed. Patients with this abnormality are at increased risk of VTE [18].

Objective of the research

To determine other factors (body mass index status, hypertension and diabetes mellitus) associated with being at risk of

VTE based on platelet count, d-dimer and fibrinogen levels among women on injectable contraceptives

RATIONALE FOR STUDY

Based on departmental records, injectable contraceptive use is on the increase at the University of Port Harcourt Teaching Hospital and Braithwaite Memorial Hospital. There are some reports of an increased risk of thrombosis in women on injectable contraceptives. There is limited data on the thrombotic risk of Nigerian women on injectable contraceptives. This study

seeks to assess the risk of venous thromboembolism in women on injectable contraceptives living in Port Harcourt attending University of Port Harcourt Teaching Hospital and Braithwaite Memorial Hospital family planning unit, thereby providing a baseline data for monitoring women on injectable contraceptives.

MATERIALS AND METHODS

Study Location

This study was conducted at the University of Port Harcourt Teaching Hospital (UPTH), a Federal Government tertiary institution and Braithwaite Memorial Specialist Hospital (BMSH), a state owned tertiary institution. Both tertiary health institutions are situated

in Port Harcourt, Rivers State and have several specialties including Haematology, Obstetrics & Gynaecology and Paediatrics. These hospitals also serve as the main referral centres for Rivers State and its environs.

STUDY DESIGN

This is a cross sectional comparative study.

STUDY POPULATION

Women on injectable contraceptives attending the family planning clinic in two tertiary health care centres - University of Port Harcourt Teaching Hospital and Braithwaite Memorial Hospital in Port Harcourt metropolis

comprised the subjects. While the controls comprised of apparently healthy women between the ages of 18 and 45 who were not on any form of contraceptives and who gave their informed consent to participate.

Inclusion Criteria for the Cases

1. Attendees of the family planning clinic on injectable contraceptives.
2. Non-pregnant women of reproductive age (18-45) who have been on injectable contraceptives

Exclusion Criteria for the Cases

1. Women with chronic illness (except hypertension and diabetes mellitus), malnutrition or on anticoagulant therapy.
 2. Past and present history of thrombosis
- The controls were apparently healthy women (except those with a history of

diabetes mellitus or hypertension) between the ages of 18-45 who gave consent to participate in the study and

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had never been on hormonal contraceptives.

ETHICAL CONSIDERATION

Ethical approval was obtained from University of Port Harcourt Teaching Hospital. The study objectives and procedure for sample collection and follow up was explained to each

participant before signing the consent form. Confidentiality and animosity were maintained in the course of the research.

SAMPLE SIZE ESTIMATION

Consecutive sampling was used

The sample size was calculated from the formula $n = Z^2pq/d^2$. Where n = the required sample size (when population is >10,000). Z= the standard normal deviation, usually set at 1.96 which corresponds to 95% confidence interval. P=the proportion of the target population estimated to have a particular characteristics. In this research, data from United Kingdom revealed that 3% of women are on injectables, there are varying or controversial literature concerning the number of women on injectable contraceptives in Nigeria. Some studies

gave 7.9% while others gave 3.8%. However due to absence of local prevalence in Port Harcourt, 5% prevalence was used to calculate the sample size. $Q = 1.0 - p = 1.0 - 0.05 = 0.95$ D = the degree of accuracy which is usually set at 0.05. With this formula $n = 72$ Applying this formula, a minimum sample size of 72 was determined. However given 10% non - response rate, a minimum sample size of appropriately 80 was recruited into the study. The control sample was taken from women within the ages of 18-45 years that are not on hormonal contraceptives.

SAMPLE COLLECTION AND PREPARATION

After filling the questionnaire, venous blood was collected by venipuncture following standard sterile procedure into 2 vacuum tubes. Blood measuring 5ml was put into an EDTA bottle and 4.5ml into a bottle containing 0.5ml of 0.129M sodium citrate to ensure adequate blood-anticoagulant ratios. Samples were properly mixed after sample collection. Samples were also collected for C-reactive protein (CRP)

and erythrocyte sedimentation rate (ESR) levels assessment, as controls for d-dimer and fibrinogen testing to rule out acute phase reaction. Those with high CRP or ESR values were excluded. The sample in the EDTA bottle was used to evaluate the platelet count of the participants. Samples in the sodium citrate bottle which was for fibrinogen assay and d-dimer testing were centrifuged at 3500 rpm for seven

minutes and stored at room temperature. If testing was not done within four hours of collection, the

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plasma was separated immediately and stored at -20°C for two weeks

Materials

- 1) Auto haematology analyzer (model: BC0800)
- 2) Glass test tubes
- 3) Stop clock
- 4) Water bath
- 5) Precision pipettes (capable of delivering between 0-200ul)
- 6) Racks
- 7) Microplate reader capable of measuring absorbance at 450nm
- 8) Precision pipettes to deliver 2ul to 1ml volumes
- 9) Adjustable 1-25ml pipettes for reagent preparation
- 10) 100ml and 1litre graduated cylinders
- 11) Absorbent paper
- 12) Distilled water or deionized water
- 13) Log-log graph paper or computer and software for ELISA data analysis
- 14) Test tubes to prepare standard or sample dilutions

Reagent

- 1) Calibration/standard plasma
- 2) Control plasma
- 3) Bovine Thrombin solution
- 4) Imidazole Buffer
- 5) Distilled water
- 6) D-dimer Microplate of 96 wells coated with antihuman d-dimer
- 2) Wash Buffer Concentrate
- 3) Standard Protein of Human d-dimer
- 4) Detection Antibody d-dimer of biotinylated anti-human d-dimer
- 5) HRP-Streptavidin Concentrate
- 6) TMB One-step Substrate Reagent
- 7) Stop solution (Sulfuric acid)
- 8) Assay Diluent buffer

METHODOLOGY

D-Dimer and Fibrinogen testing was carried out in duplicate for all the samples. Full blood count was carried out on the sample in an EDTA bottle using an autoanalyzer. The normal reference range of platelet count is $90-350 \times 10^9/L$. Fibrinogen Assay.

Fibrinogen Assay was done using a modified Clauss Fibrinogen Reagent Kit. A modified Clauss Fibrinogen Reagent Kit has a high thrombin concentration that makes the test virtually insensitive to heparin (10 I.U./mL) and enhance clot detection.

Fibrinogen assay procedure

- 1) Standard plasma was diluted with imidazole buffer solution. This gave a range of fibrinogen concentration (i.e. 1in 5, 1in 10, 1 in 20 and 1in 40).
- 2) 200ul of the solution was warmed in a water bath, at 37°C.
- 3) 100ul of thrombin solution was added and the clotting time measured.

- 4) A plot of the clotting time against fibrinogen concentration in seconds and g/l respectively was made on a log/log graph paper.
- 5) 1 in 10 dilution of each test samples was made with imidazole buffer solution.
- 6) 200ul of this test sample dilutions was clotted with 100ul of thrombin solution and clotting times was noted.
- 7) The fibrinogen concentrations of each test sample was read off the graph.

Normal range approximately 1.5 -4.0g/l

D - Dimer Assay

D-dimer testing was measured with IMUCLONE® D-dimer ELISA method following the manufacturers instruction

- 1) 100ul of sample was added to each well
- 2) The microplate was incubated at room temperature for 2.5 hours
- 3) The microplate was washed 4 times with wash solution, decanted and blotted with absorbent paper.
- 4) 100ul prepared biotin antibody was added to each well.
- 5) The microplate was then incubated at room temperature for 1 hour.
- 6) The microplate was once again washed 4 times with wash solution, decanted and blotted with absorbent paper.
- 7) 100ul prepared Streptavidin solution was then added.
- 8) Thereafter the microplate was incubated at room temperature for 45 minutes.
- 9) Subsequently it washed 4 times with wash solution, decanted and blotted with absorbent paper.
- 10) 100ul TMB One-Step Substrate Reagent was added to each well.
- 11) The microplate was then incubated at room temperature in the dark for 30 minutes.
- 12) 50ul of Stop solution was added to each well.
- 13) The Absorbance was read at 450nm immediately.

Plasma normal level < 200ng/ml

PRECAUTIONS

- 1) Contact was avoided with the skin and mouth, even when the reagent did not contain reactive components.
- 2) Donor blood and materials used for the preparations were handled as potentially infectious agents, although the blood had been found to be sero-negative to HIV, HCV and HbsAg

DATA ANALYSIS

Data entry and analysis were done using the Statistical Package for Social

Sciences (SPSS) software version 22.0. The quantitative variables such as d-

dimer, fibrinogen and platelet values were summarized as means ± standard deviation while frequencies and proportions were used to summarize categorical variables. Differences in means between groups (women on injectable and controls) were

compared using the student t-test. Chi-square and Fishers exact test were used as appropriate to compare differences in proportions. Probability values less than 0.05 (p < 0.05) were considered as significant.

RESULTS

A total of 160 women were recruited for this study, comprising of 80 women on injectable contraceptives (cases) and 80 women not on any form of

contraceptives (controls). Both groups were within the 18-45 years age bracket. The study was conducted over a period of 24 months (July 2015 to June 2017).

Social Demographics

The largest number of cases (39 cases) were found in the 31-40 years group, constituting 48.8% of that population. The 21-30 year group constituted the largest number (48) among the controls. There was a significant difference between the ages of the cases and controls (p-value- 0.0001). Ninety nine

percent of cases were married while 85.00% of controls were single. Tertiary level of education was attained by 46 (57.50%) of the cases while all the controls had tertiary level of education. Eighty five percent of the cases were employed while 80.0% of the controls were unemployed as shown in table I

Body mass index of study population

The mean BMI of the cases was 24.31±4.40 kg/m² while that of the controls were 24.21±5.22 kg/m². The difference in BMI between the cases and controls was not significantly different (p = 0.906). Majority of the cases (56.2%) and controls (60.0%) had their BMI

within the normal range of (18.50 - 24.99kg/m²). The BMI was greater than 30kg/m² in 7.5% of cases and 11.2% of controls. The difference between the cases and controls was not statistically significant (p = 1.702) as shown in table II.

Medical Morbidity

Among the cases, nine (11.2%) were diabetic while one (1.2%) of the controls were diabetic. This was statistically significant (p = 0.009). Twelve cases (15.0%) were hypertensive while all the

controls were not. The percentage of cases that were hypertensive when compared to the controls were also found to be significantly different (p = 0.0001) as shown in table III.

Relationship between BMI and risk of venous thromboembolism among cases

Risk of a thrombotic event was only recorded in 1(4.5%) of the over - weight

cases. This is not statistically significant (P = 0.438) as shown in Table IV.

Relationship between clinical history (history of hypertension and diabetes mellitus) and risk of VTE among cases

Among the cases, no diabetics was at risk of VTE, while 1.4% of non - diabetics were at risk. P = 1.00. Also no hypertensive was at risk of VTE, while

1.5% of non-hypertensives were at risk of VTE. These variables were not significantly high, P = 1.000, Table V.

Summarized risk factors in cases and controls for VTE

In this study, one case was at risk of VTE based on a high d-dimer (240.48g/l), high platelet count

(354x10⁹/l) and a high body mass index. Three controls were at risk of VTE. One had a normal BMI, but a high d-dimer

(211.80g/l) and platelet count (384x10⁹/l). The second control had a high BMI, high d-dimer (208.91g/l), and high platelet count (408x10⁹/l), while

the last control had a high BMI and high platelet count (481x10⁹/l) as shown in tableVI

Table I: Socio-demographic Characteristics of Respondents

	Cases n (%)	Control n (%)	Total n (%)
Age in years			
≤20 years	0 (0.00)	19 (23.80)	19 (11.90)
21 - 30 years	19 (23.80)	48 (60.00)	67 (41.90)
31 - 40 years	39 (48.80)	7 (8.80)	46 (28.80)
>40 years	22 (27.50)	6 (7.50)	28 (17.50)
	<i>Chi square = 62.956; p-value = 0.0001*</i>		
Marital status			
Single	1 (1.20)	68 (85.00)	69 (43.10)
Married	79 (98.80)	12 (15.00)	91 (56.90)
	<i>Chi square = 114.388; p-value = 0.0001*</i>		
Educational level			
Primary	9 (11.30)	0 (0.00)	9 (5.70)
Secondary	25 (31.20)	0 (0.00)	25 (15.70)
Tertiary	46 (57.50)	80 (100.00)	126 (78.80)
	<i>Fisher's exact test = 50.030; p-value = 0.0001*</i>		
Employment status			
Unemployed	12 (15.00)	64 (80.00)	76 (47.50)
Employed	68 (85.00)	16 (20.00)	42 (26.20)
	<i>Chi square = 79.960; p-value = 0.0001*</i>		

*Statistically significant

Table II: BMI Category of Respondents

BMI category (kg/m ²)	Cases n (%)	Control n (%)	Total n (%)
Underweight (<18.50)	7 (8.80)	6 (7.50)	13 (8.10)
Normal (18.50 - 24.99)	45 (56.20)	48 (60.00)	93 (58.10)
Over-weight (25.00 - 29.99)	22 (27.50)	17 (21.20)	39 (24.40)
Obese (≥30.00)	6 (7.50)	9 (11.20)	15 (9.40)
<i>Mean (±SD)</i>	<i>24.31±4.40</i>	<i>24.21±5.22</i>	

Chi square = 1.415; p-value =1.702

BMI - Body Mass Index

Table III: Medical Morbidity of Respondents

Variables	Cases n (%)	Control n (%)	Total n (%)
Diabetes mellitus			
Yes	9 (11.20)	1 (1.20)	10 (6.20)
No	71 (88.80)	79 (98.80)	150 (93.80)
<i>Chi square = 6.827; p-value =0.009*</i>			
Hypertension			
Yes	12 (15.00)	0 (0.00)	12 (7.50)
No	68 (85.00)	80 (100.00)	148 (92.50)
<i>Chi square = 12.973; p-value =0.0001*</i>			

*Statistically significant

Table IV: Relationship between BMI and Risk of VTE among Cases

BMI	Risk of VTE		Total n (%)
	Yes n (%)	No n (%)	
Underweight (<18.50)	0 (0.00)	7 (100.00)	7 (100.00)
Normal (18.50 - 24.99)	0 (0.00)	45 (100.00)	45 (100.00)
Over-weight (25.00 - 29.99)	1 (4.50)	21 (95.50)	22 (100.00)
Obese (≥30.00)	0 (0.00)	6 (100.00)	6 (100.00)
Total	1 (1.20)	79 (98.80)	80 (100.00)

Fisher’s exact test = 3.999; p-value = 0.438 BMI - Body Mass Index

Table V: Relationship between Clinical History and Risk of VTE among Cases

Variables	Risk of VTE		Total n (%)
	Yes n (%)	No n (%)	
Diabetes mellitus			
Yes	0 (0.00)	9 (100.00)	9 (100.00)
No	1 (1.40)	70 (98.60)	71 (100.00)
	<i>p-value = 1.000</i>		
Hypertension			
Yes	0 (0.00)	12 (100.00)	12 (100.00)
No	1 (1.50)	67 (98.500)	68 (100.00)
	<i>p-value = 1.000</i>		

*History of diabetes and hypertension

Table VI: Summarized risk factors in cases and controls for VTE

s/no	Group	Age category	BMI value(category)	Hypertensive	Diabetic	D-dimer value	Fibrinogen value	Platelet count
1	Case	21 - 30 years	26.17 kg/m ² (Overweight)	Yes	No	240.48 g/l	3.395 g/l	354 X 10 ⁹ /L
2	Control	≤20 years	23.23 kg/m ² (Normal)	No	No	211.80 g/l	0.905 g/l	384 X 10 ⁹ /L
3	Control	≤20 years	25.71 kg/m ² (Overweight)	No	No	208.91 g/l	3.352 g/l	408 X 10 ⁹ /L
4	Control	21 - 30 years	25.63 kg/m ² (Overweight)	No	No	100.90 g/l	1.095 g/l	481 X 10 ⁹ /L

BMI - Body Mass Index

DISCUSSION

Venous thromboembolism is associated with high morbidity and mortality rates. Injectable contraceptives are generally believed not to be associated with any thrombotic risk, but there are conflicting reports on thrombotic risk in women on injectable contraceptives. Some researchers have reported an increased risk of venous thromboembolism [1, 2, 3]. However most of the available studies were conducted in non-African populations. There is paucity of studies on this in our environment. In this study of apparently healthy women, between the ages of 18 and 45 years, the mean ages of the cases and controls were significantly different with the cases being older than the controls, although they were both within the age range specified for the study. More married women were on injectable

contraceptives than those in the control group, only one single woman was on injectable contraceptives. There was no significant difference between their mean BMI. Majority in both groups had normal BMI. This is similar to Van Hylckama Vlieg et al's (2010) [19] case - control study in a large population which observed that contraceptive users were of older age than non-users, but noted no significant difference between the mean BMI of patients and control. This is in contrast to the observation made by Vaneska et al (2017) [20] who noticed no significant difference with respect to this variable. In this study the number of cases that were hypertensive and diabetic were significantly higher than controls. This may be related to the higher mean age of the case group compared to the control group because

injectable contraceptives do not contain estrogen which is implicated in increased risk of hypertension and diabetes [14]. Hypertension and diabetes mellitus are independent predictors of venous thromboembolism [16]. It is important to note that the comparative risk of VTE was not significantly different between both groups. There are various risks for VTE which include increased age, obesity, use of OCPs, and cardiovascular diseases. In this study, one case was at risk for VTE based on high d-dimer and platelet count. She

Okpara also had a high BMI but was neither diabetic nor hypertensive. Her age was between 21 - 30 years. Therefore she had multiple risks for VTE (high d-dimer, platelet count and BMI) although from our findings the use of injectable contraceptives may not have added to that risk. More controls had high BMI's, d-dimer and platelet counts. But nor was diabetic nor hypertensive. Further studies need to be done to verify this findings and also to confirm if injectable contraceptives play a protective role.

CONCLUSION

This study found no correlation between the use of injectable contraceptives and the risk of venous thromboembolism. In conclusion, women on injectable

contraceptives in Port Harcourt Nigeria do not have a higher risk of VTE than non-contraceptive users.

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